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DECREASED SUSCEPTIBILITY OF *NEISSERIA GONORRHOEAE* TO FLUOROQUINOLONES — ONTARIO, 1992-1994

Introduction

Antibiotic-resistant isolates of *Neisseria gonorrhoeae* remain an important public health problem. Fluoroquinolones, such as ciprofloxacin, have excellent penetration into the genitourinary tract[1] and have been shown to be highly active against *N. gonorrhoeae*, including penicillinase-producing strains (PPNG)[2,3]. However, strains with decreased susceptibility to fluoroquinolones have been reported in various parts of the world[4,5,6,7]. Six isolates of *N. gonorrhoeae* from Alberta, British Columbia and Newfoundland with minimum inhibitory concentrations (MICs) of 2.0 mg/L to norfloxacin and 0.25 mg/L to ciprofloxacin were characterized by Yeung and Dillon in 1991[8]. These reports prompted us to investigate isolates submitted to our laboratory. The present communication describes the results of the study of 47 isolates with decreased susceptibility to quinolones during the period 1992 to June 1994.

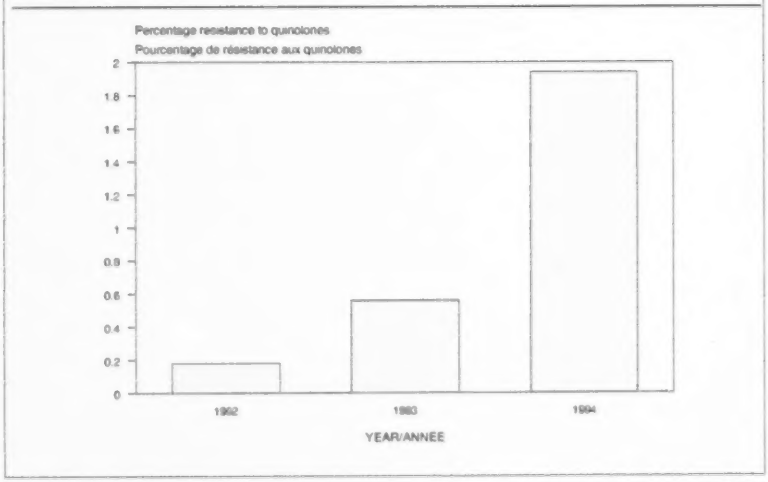
Methods

Antimicrobial susceptibility was performed by the agar dilution method. GC agar base (Difco) enriched with 1.5% lysed horse blood and 1% Kellogg's supplement was used for all antimicrobial agents. The inoculum was prepared and plates inoculated as outlined in NCCLS Document M7-A3[9]. The concentrations of antibiotics tested were as follows: penicillin, 0.06, 0.12, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 mg/L; tetracycline, 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 mg/L; erythromycin, 0.5, 1.0, 2.0, 4.0 and 8.0 mg/L; ciprofloxacin, 0.06, 0.12, 0.25, 0.5, 1.0 and 2.0 mg/L; norfloxacin, 0.5, 1.0, 2.0 and 4.0 mg/L; cefixime, 0.25 mg/L; ceftriaxone, 0.25 mg/L; and spectinomycin, 16.0 and 32.0 mg/L.

Results and Discussion

Figure 1 shows the percentage of isolates of *N. gonorrhoeae* that had decreased susceptibility to quinolone agents between 1992

FIGURE 1
***Neisseria gonorrhoeae* resistance to quinolones — Ontario, 1992-94**



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and June 1994. Of the 3,285 strains investigated in 1992, 6 isolates (0.18%) were identified. During 1993 there was a three-fold increase, 15 of 2,663 (0.56%), over the previous year, and in the first six months of 1994, 26 of 1,340 (1.94%) showed decreased susceptibility to quinolones, representing a 10-fold increase over 1992.

Table 1 illustrates the distribution of the different categories of resistant phenotypes between 1992 and June 1994. In the first year of the study (1992), the majority of isolates with reduced susceptibility to quinolones were penicillin-resistant, including two which were PPNG. None of the isolates were penicillin-sensitive. During 1993 we observed the emergence of a cluster of isolates with marginally increased MICs to quinolones (ciprofloxacin 0.12 mg/L), and susceptibility to penicillin (MIC ≤ 0.06 mg/L) and other antimicrobial agents. Isolates in 1993 and 1994 (to June) were divided mainly between the penicillin-sensitive strains and those which showed chromosomally mediated resistance to penicillin (MIC ≥ 2.0 mg/L).

Table 1
Comparison of the (number) percentage of isolates of *Neisseria gonorrhoeae* with decreased susceptibility to ciprofloxacin — 1992 to June 1994

Susceptibility	Penicillin MIC	Ciprofloxacin MIC	1992	1993	1994 (to June)
Sensitive	≤ 0.06 mg/L	0.12 mg/L	(0/6) 0%	(8/15) 53.3%	(10/26) 38.5%
Moderate sensitivity	0.12 – 1.0 mg/L	0.12 – 0.25 mg/L	(1/6) 16.6%	(1/15) 6.7%	(5/26) 19.2%
Resistant	≥ 2.0 mg/L	0.25 – 0.5 mg/L	5/6 (83.3%)*	(6/15) 40.0%	(11/26) 42.3%

* two isolates were PPNG

The MICs of the 47 strains for each antimicrobial agent tests are shown in Table 2. Twenty-two isolates, which were penicillin-resistant with ciprofloxacin MIC ranging from 0.25 to 0.5 mg/L, also displayed reduced susceptibility to norfloxacin (MIC 2.0 - > 4.0 mg/L). All of these isolates were resistant to tetracycline (MIC 2.0 - 8.0 mg/L) and all but one isolate was resistant to erythromycin. Eighteen isolates were penicillin-susceptible with ciprofloxacin MIC of 0.12 mg/L and norfloxacin MIC of 1.0 mg/L. These isolates were all sensitive to erythromycin and moderately sensitive to tetracycline. The 7 remaining isolates had ciprofloxacin and norfloxacin MICs ranging from 0.12 to 0.25 mg/L and 1.0 to 4.0 mg/L, respectively. All but one isolate was resistant to erythromycin and tetracycline and all showed intermediate resistance to penicillin. All 47 isolates were susceptible to cefixime, ceftriaxone and spectinomycin.

Table 2
In vitro activity of selected antimicrobial agents against 47 isolates of *Neisseria gonorrhoeae* with decreased susceptibility to fluoroquinolones

Antimicrobial agent	MIC range (mg/L) for		
	Penicillin-sensitive strains (n = 18)	Penicillin-moderately sensitive strains (n = 7)	*Penicillin-resistant strains (n = 22)
Penicillin	≤ 0.06	0.25 – 1.0	2.0 – >16
Ciprofloxacin	0.12	0.12 – 0.25	0.25 – 0.5
Norfloxacin	1.0	1.0 – 4.0	2.0 – > 4.0
Erythromycin	≤ 0.5	1.0 – 4.0	1.0 – 8.0
Tetracycline	≤ 0.5 – 1.0	0.5 – 4.0	2.0 – 8.0

* two isolates were penicillinase-producing *N. gonorrhoeae* (PPNG). All isolates were susceptible to cefixime, ceftriaxone and spectinomycin (MICs < 0.25 mg/L, < 0.25 mg/L, and ≤ 32 mg/L, respectively).

The majority of isolates were recovered from male patients; however, 13 of 47 (27.7%) were from female patients. During 1992 and 1993 the proportion of isolates was 16.6% and 13.3%, respectively; an increase to 38.5% has been found during the first 6 months of 1994.

The present study has demonstrated that reduced susceptibility to quinolone agents was associated with three populations of *N. gonorrhoeae* in Ontario. One population exhibited marginally increased MICs to fluoroquinolones and general susceptibility to other antimicrobial agents. The second consists of a heterogeneous group showing resistance to other antimicrobials, such as penicillin, tetracycline and erythromycin; this group includes two PPNG isolates. The third population showed moderate susceptibility to penicillin, a more diverse pattern of resistance to other antibiotics, and MICs to quinolones ranging from those associated with the penicillin-sensitive to those associated with the penicillin-resistant strains. These results differ from those of a number of studies that reported only PPNG isolates with quinolone insensitivity[5,7,8]. It is possible that the epidemiology of *N. gonorrhoeae* strains with decreased susceptibility to quinolones is changing.

Acknowledgements: The authors acknowledge the assistance of the staff of the STD and Antimicrobial susceptibility laboratories.

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Editorial Comment

The 1992 edition of the *Canadian Guidelines for the Prevention, Diagnosis, Management and Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults*[1] introduced the use of fluoroquinolones as first-line therapy for the treatment of uncomplicated gonorrhea[1]. The change in treatment regimen was precipitated by surveillance of antibiotic resistance, which showed an increasing prevalence of plasmid-mediated penicillin resistance (PPNG).

Fluoroquinolones replaced penicillin as the first-line of treatment for uncomplicated gonorrhea because they treat **all** gonococcal infections as if they were resistant to penicillin. Amoxicillin, however, is recommended as the alternative regimen with a cautionary caveat that it should only be used in areas with active monitoring for resistance to penicillin AND if the percentage of penicillin-resistant isolates does not exceed 3% AND if the infection was acquired in the same geographic area.

The current recommended first-line therapy for uncomplicated gonorrhea is **ceftriaxone 250 mg intramuscularly in a single dose PLUS doxycycline 100 mg orally twice daily for 7 days OR tetracycline 500 mg orally four times a day for 7 days because treatment of gonorrhea should always include treatment for co-infection with *Chlamydia***. The recommended oral regimens are cefixime 800 mg orally in a single dose; ciprofloxacin 500 mg orally in a single dose; or ofloxacin 400 mg orally in a single dose.

The 1992 Guidelines are currently being updated. It is quite likely after a thorough review that penicillin, amoxicillin or ampicillin will no longer be recommended as therapy for gonococcal infection.

Changes in national treatment guidelines should reflect changes in patterns of microbial resistance, which are monitored via national surveillance of isolates of *N. gonorrhoeae*.

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HUMAN T-CELL LYMPHOTROPIC VIRUS, TYPE I (HTLV-I) REPORTED IN BRITISH COLUMBIA

Background

The human T-lymphotropic viruses type I (HTLV-I) and type II (HTLV-II) are closely related, but distinct retroviruses, that can infect humans. They are related to, but differ from, the human immunodeficiency viruses that cause AIDS.

HTLV-I infection is endemic in southwestern Japan, the Caribbean basin, Melanesia, and in parts of Africa. In some areas where HTLV-I infection is endemic, prevalence rates as high as 15% have been reported in the general population. Seroprevalence increases with age; in older age groups, rates are usually higher in women than in men. In the United States, HTLV-I/II seroprevalence rates among volunteer blood donors average 0.016%. Approximately one-half of HTLV-I/II seropositive blood donors in the U.S. are infected with HTLV-I.

Transmission of HTLV-I occurs from mother to child primarily by breast feeding; by sexual contact; by blood transfusion; and by the sharing of contaminated needles.

Two diseases have been associated with HTLV-I: adult T-cell leukemia/lymphoma (ATLL) and a chronic degenerative neurologic disease, HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP). Recently, infective dermatitis, a chronic eczema associated with *Staphylococcus aureus* and beta-hemolytic *Streptococcus* has been reported in HTLV-I infected Jamaican children. The full spectrum of HTLV-I associated diseases may include other disorders, such as polymyositis, chronic arthropathy, panbronchiolitis, and uveitis.

Transmission of HTLV-II is similar to I but has not yet been clearly associated with any diseases.

Adult T-cell leukemia/lymphoma has been estimated to occur in 2% to 4% of individuals infected with HTLV-I in regions where HTLV-I is endemic and where early childhood infection is common. It occurs most frequently among persons aged 40 to 60 years, suggesting that a latent period as long as a few decades is required for the disease to develop.

Fewer than 10% of HTLV-I infected persons develop the neurologic disease; it is believed to be immunologically mediated and it affects women more than men. The latency period for this disease is shorter than for leukemia; cases have been associated with blood transfusion, with a median interval of 3.3 years between transfusion and development of the disease[1].

HTLV-I in Aboriginal Patients in British Columbia

In November, 1993, a Vancouver neurologist published a report on four cases of HAM/TSP and one case of ATLL in aboriginal British Columbians, the first reported cases in native-born Canadians[2]. In anticipation of this report, a meeting of national and international communicable disease experts was convened by the Medical Services Branch of Health Canada in Vancouver on 16 to 17 November, 1993. This meeting provided up-to-date information on HTLV and the basis for further action related to HAM/TSP and ATLL.

In December, 1993, a tripartite steering committee was formed with membership from the First Nations Summit Health Committee, the Provincial Ministry of Health, and Medical Services Branch, with the responsibility to provide direction on HTLV-related issues in British Columbia. A workshop was held 26 to 27 January, 1994. Participants included federal and provincial community health nurses and community health representatives servicing Indian reserves in British Columbia.

At the same time as the workshop was occurring, information was distributed throughout British Columbia to medical health officers, physicians, all chiefs and tribal council members, community health representatives not able to attend the workshop, and the media.

The objective of this approach was to ensure that information on HTLV-I was widely circulated to health care providers and the general public in order to raise general awareness of the public health implications of the virus, and to assist in the identification of new cases previously unidentified.

Evidence to date indicates that HTLV-I associated disease is not common in B.C., although surveillance studies are underway to confirm this finding. The routes of transmission of HTLV-I are similar to HIV; therefore, the programs currently in place to control HIV should contribute to lessening the risk of transmission of HTLV-I as well. Although breast feeding is a route of transmission, the overall benefits of breast feeding compared to the risk of HTLV-I transmission indicate that screening for HTLV-I is not warranted before breast feeding. The advantages and disadvantages of breast feeding should be discussed with mothers known to be positive for HTLV-I.

Future Action Related to HTLV-I

The Laboratory Centre for Disease Control in Ottawa will coordinate national surveillance initiatives. In particular, neurologists, and practitioners working with native patients are advised to watch for HAM/TSP, which may mimic multiple sclerosis.

The tripartite steering committee in B.C. will recommend appropriate surveillance initiatives in cooperation with relevant agencies. Regular updates will be provided as appropriate.

Detailed information can be obtained from **Dr. David Martin, Health Canada, Medical Services Branch, Pacific Region, Suite 540, 757 West Hastings Street, Vancouver, B.C., V6C 3E6 (Tel: 604-666-6155; FAX: 604-666-6024).**

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Source: *D Martin, MD, Programs Medical Officer, Medical Services Branch, R Mathias, MD, Associate Professor, Department of Health Care and Epidemiology, University of British Columbia, Vancouver, British Columbia; J Wortman, MD, Consultant, AIDS and STD, Medical Services Branch, Ottawa, Ontario.*

SURVEILLANCE PROGRAM FOR HTLV IN CANADA

In response to a request from the Indian and Northern Health Services Directorate of the Medical Services Branch, the Laboratory Centre for Disease Control (LCDC) introduced in mid-May, 1994, a national surveillance system for HTLV. This system was instituted following the discovery of the first cases of syndromes associated with human T-lymphotropic virus type I infection (HTLV-I), HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP), and adult T-cell leukemia/lymphoma (ATLL) among native Canadians, specifically among aboriginals on the west coast of Canada. The primary purpose of this surveillance system is to document the problem of HTLV-I infection and, secondarily, to collect basic information on HTLV-II infection.

All physician members of the Canadian Neurological and Hematology Societies, and of the Association of Medical Oncologists have been personally contacted and asked to report, anonymously, all known cases of myelopathy associated with HTLV-I, HAM/TSP and ATLL that they have encountered, regardless of date of diagnosis. For each of these cases, the physician has been requested to complete an epidemiologic questionnaire.

Provincial laboratories have been asked to include, routinely, an epidemiologic questionnaire with all positive results of HTLV-I or HTLV-I/II sent to physicians. It has also been requested that the laboratories send copies of the questionnaire to physicians who have received positive results back to January 1993. Each laboratory has also been requested to report, anonymously, all known HTLV-I, HTLV-I/II and HTLV-II positive results since 1 January, 1993, in addition to certain basic demographic data.

All of this surveillance information will be received and analyzed by the Division of Sexually Transmitted Diseases, Bureau of Communicable Disease Epidemiology, LCDC. A report will be sent to each participant in the surveillance program and published in the *Canada Communicable Disease Report.*

Source: *A Yergeau, MD, Field Epidemiologist, P Gully, MB, ChB, (formerly) Chief, Division of Sexually Transmitted Diseases, Bureau of Communicable Disease Epidemiology, LCDC, Ottawa, Ontario.*

OUTBREAK OF *SALMONELLA ENTERITIDIS* ASSOCIATED WITH NATIONALLY DISTRIBUTED ICE CREAM PRODUCTS — MINNESOTA, SOUTH DAKOTA, AND WISCONSIN, 1994

From 19 September through 10 October, 1994, a total of 80 confirmed cases of *Salmonella enteritidis* (SE) infection were reported to the Minnesota Department of Health (MDH); in comparison, 96 cases were reported statewide during all of 1993. Cases were characterized by diarrhea, abdominal cramps, and fever. Recent increases in SE cases also were reported from South Dakota (14 cases during 6 September to 7 October, compared with 20 cases during all of 1993) and Wisconsin (48 cases during 6 September to 7 October, compared with 187 during all of 1993). This report summarizes preliminary findings from the outbreak investigation.

On 5 and 6 October, to assess potential risk factors for infection, the MDH conducted a case-control study of 15 cases and 15 age- and neighborhood-matched controls. A case was defined as culture-confirmed SE in a person with onset of illness during September. Eleven case-patients (73%) and two controls (13%) reported consumption of Schwan's ice cream within 5 days of illness onset for case-patients and a similar period for controls (odds ratio = 10.0; 95% confidence interval = 1.4 - 434.0).

On 7 and 9 October, the MDH issued press releases informing the public of this problem and advising persons who had been ill since 1 September and who had consumed Schwan's ice cream to contact the health department. During 8 to 11 October, a total of 2,014 persons who had consumed suspected products and had been ill with diarrhea contacted the MDH by telephone. Samples of ice cream from households of ill persons grew SE.

Ill persons reported eating all types and flavors of ice cream products produced at the Schwan's plant in Marshall, Minnesota, including ice cream, sherbet, frozen yogurt, and ice cream sandwiches and cones; these products had production dates in August and September. The implicated products are distributed nationwide, primarily by direct delivery to homes, and are sold only under the Schwan's label. Investigations to examine the extent and causes of the outbreak are under way.

On 7 October, the company voluntarily stopped distribution and production at the Marshall plant pending further findings from these investigations.

MMWR Editorial Note: Gastroenteritis caused by *Salmonella* is characterized by abdominal cramps and diarrhea, vomiting, fever, and headache. Antimicrobial therapy is not indicated in uncomplicated gastroenteritis, which typically resolves within 1 week. Persons at increased risk for infection or more severe disease include infants; the elderly; persons with achlorhydria; those receiving immunosuppressive therapy; persons who may have received antimicrobials for another illness; and those persons with sickle-cell anemia, cancer, or acquired immunodeficiency syndrome. Complications include meningitis, septicemia, Reiter syndrome, and death.

Salmonella sp. are second only to *Campylobacter* as a cause of bacterial diarrheal illness in the United States, causing an estimated 2 million illnesses annually. Among the more than 2,000 *Salmonella* serotypes, SE has ranked first or second in frequency of isolation from humans since 1988 and accounted for 21% of reported isolates in 1993. Each year, an average of 55 outbreaks of SE infections are reported to CDC; approximately 11% of patients are hospitalized, and 0.3% die.

Preliminary findings from this outbreak indicate that the number of persons exposed to contaminated products may be substantial. Approximately 400,000 gallons of the implicated products are produced weekly and are distributed throughout the contiguous United States. Previous investigations have established the potential for large-scale outbreaks of foodborne salmonellosis; for example, in 1985, pasteurized milk produced at one dairy plant caused up to 197,000 *Salmonella* infections.

Source: *Morbidity and Mortality Weekly Report, Vol 43, No 40, 1994.*

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